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PATENT SPECIFICATION

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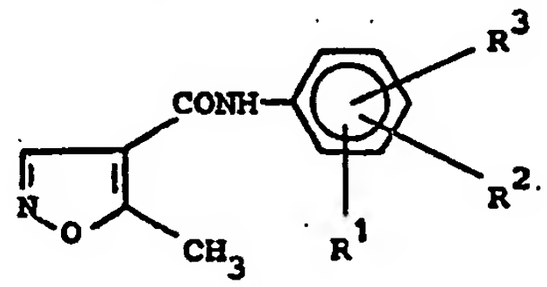
(54) 5-METHYLISOXAZOLE-4-CARBOXYLIC ACID ANILIDES HAVING PHARMACEUTICAL ACTIVITY

(71) We, HOECHST AKTIENGESELLSCHAFT, a body corporate organised according to the laws of the Federal Republic of Germany, of 6230 Frankfurt/Main 80, Postfach 80 03 20, Federal Republic of Germany, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to isoxazole derivatives and is an improvement in, or modification of, the invention of our U.K. Patent No. 1,547,452.

U.K. Patent No. 1,547,452 describes and claims 5 - methyl - isoxazole - 4 - carboxylic acid anilides of the general formula



in which R^1 and R^2, which may be identical or different, each represents a hydrogen atom; an alkyl group of 1, 2 or 3 carbon atoms, an alkoxy group of 1, 2 or 3 carbon atoms, an alkylthio group of 1, 2 or 3 carbon atoms, the alkyl groups of which may be substituted partly or totally by identical or different halogen atoms, for example, fluorine, chlorine, bromine or iodine atoms, or represents a halogen atom, for example, a fluorine, chlorine, bromine or iodine atom, or represents a nitro or cyano group or an alkoxycarbonyl group having 1, 2 or 3 carbon atoms in the alkyl moiety,

R^3 represents an alkyl group of 1, 2 or 3 carbon atoms, an alkoxy group of 1, 2 or 3 carbon atoms, an alkylthio group of 1, 2 or 3 carbon atoms, the alkyl groups of which may be substituted partly or totally by identical or different halogen atoms, for example, fluorine, chlorine, bromine or iodine atoms, or represents a halogen atom, for example, a fluorine, chlorine, bromine or iodine atom, or represents a nitro or cyano group or an alkoxycarbonyl group having 1, 2 or 3 carbon atoms in the alkyl moiety; or represents a phenyl group which may carry one or two substituents selected from fluorine, chlorine, bromine and iodine atoms, alkyl groups of 1, 2 or 3 carbon atoms and alkoxy groups of 1, 2 or 3 carbon atoms, or a phenoxy group which may carry one or two substituents selected from fluorine, chlorine, bromine and iodine atoms, alkyl groups of 1, 2 or 3 carbon atoms and alkoxy groups of 1, 2 or 3 carbon atoms; or

in which R^1 stands for a hydrogen atom, and R^2 and R^3 together represent a methylenedioxy group or, together with the phenyl ring, to which they are linked, represent a naphthalene ring;

with the proviso that R^3 does not represent a methyl group when R^1 and R^2 both represent hydrogen atoms.

We have now found that pharmacological properties are also shown by compounds of the above general formula in which at least one of the radicals R^1 to

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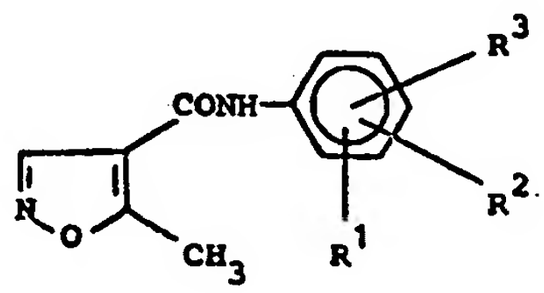
R^3 represents a carboxy or hydroxy group and the remaining group or groups, if any, have the meanings given above.

Accordingly, the present invention provides a compound of the general formula



I

in which any two or more of R^1, R^2 and R^3 may be the same or different and each represents

an alkyl radical having 1, 2 or 3 carbon atoms, an alkoxy radical having 1, 2 or 3 carbon atoms, or an alkylthio radical having 1, 2 or 3 carbon atoms, each of which radicals may be unsubstituted or completely or partially substituted by one or more of the same or different halogen atoms;

a halogen atom;

a nitro group;

a cyano group;

an alkoxycarbonyl radical having 1, 2 or 3 carbon atoms in the alkyl moiety;

a hydroxy group;

a carboxy group; or

a hydrogen atom;

and in which R^2 and R^3 together may represent a methylenedioxy group or, together with the phenyl ring carrying them, a naphthalene ring;

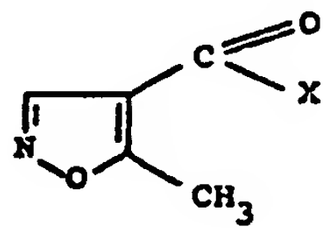
and in which if one of R^1 to R^3 represents a hydrogen atom, one other may represent a phenyl radical which may be unsubstituted or substituted in each case once or twice by fluorine, chlorine, bromine or iodine or by alkyl having 1, 2 or 3 carbon atoms or alkoxy having 1, 2 or 3 carbon atoms, or may represent a phenoxy radical which may be unsubstituted or substituted in each case once or twice by fluorine, chlorine, bromine or iodine or by alkyl having 1, 2 or 3 carbon atoms or alkoxy having 1, 2 or 3 carbon atoms; and wherein at least one of R^1 to R^3 represents a carboxy or hydroxy group.

One or both of R^1 and R^2 may represent a hydrogen atom and if one represents a hydrogen atom, R^3 additionally may represent a phenyl radical which may be unsubstituted or substituted in each case once or twice by a fluorine, chlorine, bromine or iodine atom, by an alkyl radical having 1, 2 or 3 carbon atoms, or by an alkoxy radical having 1, 2 or 3 carbon atoms, or may represent a phenoxy radical which may be unsubstituted or substituted in each case once or twice by a fluorine, chlorine, bromine or iodine atom, by an alkyl radical having 1, 2 or 3 carbon atoms or by an alkoxy radical having 1, 2 or 3 carbon atoms.

The present invention also provides a salt, especially a physiologically tolerable salt, of such a compound.

Preferred compounds of the invention are those of the general formula I in which either R^1 represents a hydrogen atom or a halogen atom, e.g. a fluorine, chlorine, bromine or iodine atom, or a trifluoromethyl group, and R^2 represents a carboxy group; or R^1 represents a hydroxy group and R^2 a halogen atom, e.g. a fluorine, chlorine, bromine or iodine atom, a trifluoromethyl or carboxy group; and R^3 in each case represents a hydrogen atom.

The present invention also provides a process for the preparation of a compound of the invention of the general formula I or a salt thereof, which comprises reacting a 5 - methylisoxazole - 4 - carboxylic acid derivative of the general formula

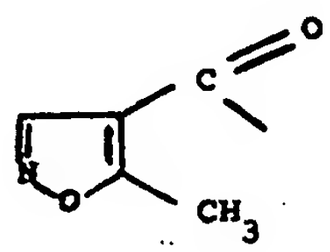


II

in which X represents

a) a halogen atom, preferably a chlorine or bromine atom;

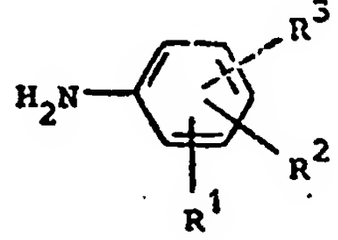
b) a YO— group in which Y represents
(i) a phenyl radical which is unsubstituted or substituted by one, two or three substituents selected from fluorine, chlorine, bromine and iodine atoms, and methyl, ethyl, methoxy, ethoxy, trifluoromethyl, nitro and cyano groups, or
(ii) the acyl radical corresponding to the formula II, that is,



II'

or

c) a ZO—CO—O— group in which Z represents a (C_1—C_4)-alkyl radical or a phenyl or benzyl radical; with an aniline of the general formula



III

in which R^1, R^2 and R^3 have the meanings given above or with a salt thereof.

Preferably, a substituted phenyl radical Y contains one substituent or two or three identical substituents.

The reaction is advantageously carried out in a dispersing agent or solvent that is inert towards the reactants, for example in a nitrile, e.g. acetonitrile; an ether, e.g. diethyl ether, tetrahydrofuran or dioxan; or an alcohol, e.g. methanol, ethanol, propanol or isopropanol.

Preferably the compound of the general formula II is the carboxylic acid chloride. It has proved advantageous in this case for the reaction to be carried out in the presence of an acid-binding agent, e.g. potassium or sodium carbonate, an alkali metal hydroxide or alcoholate, an alkaline earth metal hydroxide or alcoholate, an organic base, for example triethylamine, pyridine, picoline or quinoline, or the aniline reactant used in excess, at temperatures of from 0 to 160°C, preferably from 20 to 80°C. The reaction time may be from a few minutes to two hours.

If desired, a compound of the general formula I obtained may be converted into a salt thereof.

A 5 - methylisoxazole - 4 - carboxylic acid derivative of the general formula II required as starting material may be obtained in accordance with the method described in German Patent 634,286. In this method ethoxymethylideneacetoacetic ester is reacted with hydroxylamine to form the 5 - methyl - isoxazole - 4 - carboxylic acid ester, the ester is hydrolysed under acid conditions, preferably with a mixture of glacial acetic acid and concentrated hydrochloric acid in the ratio 1:1, and the 5 - methylisoxazole - 4 - carboxylic acid formed is converted according to a customary method into a carboxylic acid halide, ester or mixed anhydride.

The following are examples of carboxylic acid derivatives of the general formula II:

5 - methylisoxazole - 4 - carboxylic acid phenyl esters, especially the 2,4 - dichlorophenyl ester or the 2,4,6 - trichlorophenyl ester; and

5 - methylisoxazole - 4 - carboxylic acid anhydrides, especially those in which X represents the methoxycarbonyloxy radical, the ethoxycarbonyloxy radical, the phenoxycarbonyloxy radical or the benzyloxycarbonyloxy radical.

Compounds of the invention of the general formula I and their physiologically tolerable salts may be used for combating inflammations, fevers and pain.

Accordingly, the present invention provides a pharmaceutical preparation, which comprises a compound of the general formula I of the invention or a physiologically tolerable salt thereof, in admixture or conjunction with a pharmaceutically suitable carrier. Preferably the preparation is in dosage unit form.

The following Examples illustrate the invention:

1. 5-methylisoxazole-4-carboxylic acid 2-carboxy-4-chloroanilide of the general formula I

a) A solution of 0.05 mole of 5 - methylisoxazole - 4 - carboxylic acid chloride of the formula II (7.3 g) in 20 ml of tetrahydrofuran is added dropwise at room temperature, while stirring, to 0.1 mole of 2 - amino - 5 - chlorobenzoic acid of the formula III (17.2 g) dissolved in 200 ml of tetrahydrofuran. After stirring for a further 20 minutes the precipitate that has formed is suction-filtered off and extracted by boiling with 200 ml of 2N hydrochloric acid. The remaining precipitate is suction-filtered off, washed with water until neutral, and dried. In this manner 13.1 g (93% of the theoretical yield) of a colorless crystalline powder are obtained; melting point after recrystallization from ethanol: 240 to 243°C (with decomposition).

b) 0.1 mole of 2 - amino - 5 - chlorobenzoic acid of the formula III (17.2 g) and 0.1 mole of 4 - fluorophenyl 5 - methylisoxazole - 4 - carboxylate of the formula II (22.1 g) dissolved in 100 ml of tetrahydrofuran are refluxed for 80 minutes. Subsequently the precipitate is suction-filtered off and extracted by boiling with 200 ml of 2N hydrochloric acid. The remaining precipitate is suction-filtered off, washed with water until neutral and dried. In this manner 19.4 g (69% of the theoretical yield) of crystalline powder having a melting point (after recrystalization from ethanol) of 240 to 243°C (with decomposition) are obtained.

c) 0.1 mole of 2 - amino - 5 - chlorobenzoic acid of the formula III (17.2 g) and 0.1 mole of methoxycarbonyl 5 - methylisoxazole - 4 - carboxylate of the formula II (18.5 g) dissolved in 150 ml of tetrahydrofuran are refluxed for 70 minutes. Subsequently the precipitate that has formed is suction-filtered off and extracted by boiling with 200 ml of 2N hydrochloric acid. The remaining precipitate is suction-filtered off, washed with water until neutral and dried. In this manner 20.2 g (72% of the theoretical yield) of a crystalline powder having a melting point (after recrystallization from ethanol) of 240 to 243°C (with decomposition) are obtained.

The compounds listed in Table 1 were prepared in accordance with the process described above.

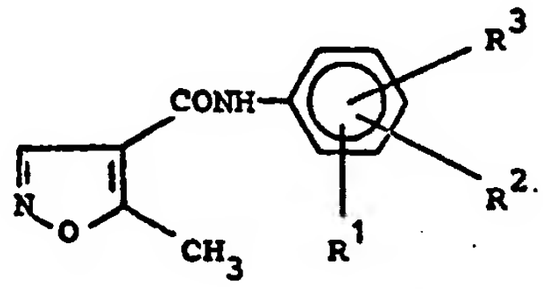
Table 1: 5 - methylisoxazole - 4 - carboxylic acid anilides of the general formula I

No.	R^1	R^2	R^3	Melting point °C
1	H	H	4-OH	160—163
2	H	H	4-COOH	128—130
3	H	3-OH	4-COOH	228—231
4	H	3-COOH	H	242—245
5	H	2-COOH	H	208—211
6	H	2-OH	5-COOH	231—234 (with decomposition)
7	H	2-OH	3-COOH	198—201 (with decomposition)
8	H	3-COOH	4-OH	247—251 (with decomposition)
9	H	2-COOH	4-OH	228—231 (with decomposition)
10	H	2-COOH	4-Cl	240—243 (with decomposition)
11	H	2-OH	4-Cl	186—188
12	H	2-COOH	5-Br	>300 (with decomposition)
13	H	2-OH	5-Cl	84—86
14	H	3-COOH	4-Cl	244—250 (with decomposition)

1. 5 - Methylisoxazole - 4 - carboxylic acid 4 - hydroxyanilide
2. 5 - Methylisoxazole - 4 - carboxylic acid 4 - carboxyanilide
3. 5 - Methylisoxazole - 4 - carboxylic acid 4 - carboxy - 3 - hydroxyanilide
4. 5 - Methylisoxazole - 4 - carboxylic acid 3 - carboxyanilide
5. 5 - Methylisoxazole - 4 - carboxylic acid 2 - carboxyanilide
6. 5 - Methylisoxazole - 4 - carboxylic acid 5 - carboxy - 2 - hydroxyanilide
7. 5 - Methylisoxazole - 4 - carboxylic acid 3 - carboxy - 2 - hydroxyanilide
8. 5 - Methylisoxazole - 4 - carboxylic acid 3 - carboxy - 4 - hydroxyanilide
9. 5 - Methylisoxazole - 4 - carboxylic acid 2 - carboxy - 4 - hydroxyanilide
10. 5 - Methylisoxazole - 4 - carboxylic acid 2 - carboxy - 4 - chloroanilide
11. 5 - Methylisoxazole - 4 - carboxylic acid 4 - chloro - 2 - hydroxyanilide
12. 5 - Methylisoxazole - 4 - carboxylic acid 5 - bromo - 2 - carboxyanilide
13. 5 - Methylisoxazole - 4 - carboxylic acid 5 - chloro - 2 - hydroxyanilide
14. 5 - Methylisoxazole - 4 - carboxylic acid 3 - carboxy - 4 - chloroanilide

WHAT WE CLAIM IS:—

1. A compound of the general formula



I

in which any two or more of R^1, R^2 and R^3 may be the same or different and each represents

an alkyl radical having 1, 2 or 3 carbon atoms, an alkoxy radical having 1, 2 or 3 carbon atoms, or an alkylthio radical having 1, 2 or 3 carbon atoms, each of which radicals may be unsubstituted or completely or partially substituted by one or more of the same or different halogen atoms;

a halogen atom;

a nitro group;

a cyano group;

an alkoxycarbonyl radical having 1, 2 or 3 carbon atoms in the alkyl moiety;

a hydroxy group;

a carboxy group; or

a hydrogen atom;

and in which R^2 and R^3 together may represent a methylenedioxy group or, together with the phenyl ring carrying them, a naphthalene ring and in which if one of R^1 to R^3 represents a hydrogen atom, one other may represent a phenyl radical which may be unsubstituted or substituted in each case once or twice by fluorine, chlorine, bromine or iodine or by (C_1—C_3) alkyl or (C_1—C_3) alkoxy, or may represent a phenoxy radical which may be unsubstituted or substituted in each case once or twice by fluorine, chlorine, bromine or iodine or by (C_1—C_3) alkyl or (C_1—C_3) alkoxy; and wherein at least one of R^1 to R^3 represents a carboxy or hydroxy group, or a salt of such a compound.

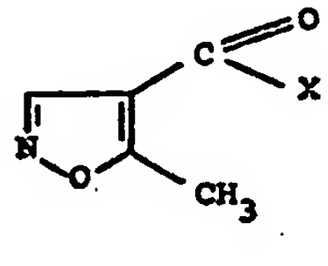
2. A compound as claimed in claim 1, wherein R^1 represents a hydrogen or halogen atom or a trifluoromethyl group and R^2 represents a carboxy group; or R^1 represents a hydroxy group and R^2 a halogen atom or a trifluoromethyl or carboxy group; whilst R^3 in each case represents a hydrogen atom.

3. A compound as claimed in claim 1 which is shown in Example 1 or Table 1 herein.

4. A salt of a compound claimed in any one of claims 1 to 3.

5. A physiologically tolerable salt of a compound claimed in any one of claims 1 to 3.

6. A process for the preparation of a compound claimed in claim 1 or a salt thereof, which comprises reacting a compound of the general formula



II

in which X represents

a) a halogen atom,

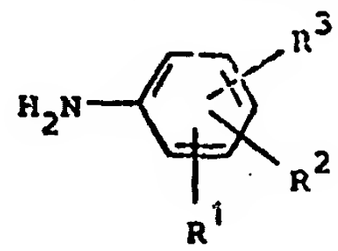
b) a YO— group in which Y represents

(i) a phenyl radical which is unsubstituted or substituted by one, two or three of the same or different substituents selected from fluorine, chlorine, bromine and iodine atoms and methyl, ethyl, methoxy, ethoxy, trifluoromethyl, nitro and cyano groups, or

(ii) the acyl radical corresponding to the formula II; or

c) a ZO—CO—O— group in which Z represents a (C_1—C_4)-alkyl radical or a phenyl or benzyl radical;

with an aniline of the general formula



III

in which R^1, R^2 and R^3 have the meanings given in claim 1, or with a salt thereof.

7. A process as claimed in claim 6, wherein the compound of the general formula II is 5 - methylisoxazole - 4 - carboxylic acid chloride, and the reaction is carried out in the presence of an acid-binding agent.

8. A process as claimed in claim 7, wherein the reaction is carried out at a temperature in the range of from 20 to 80°C.

9. A process as claimed in claim 6, wherein the compound of the general formula II is the 2,4 - dichlorophenyl ester, the 2,4,6 - trichlorophenyl ester, or the anhydride in which X represents the methoxycarbonyloxy, ethoxycarbonyloxy, phenoxycarbonyloxy or benzyloxycarbonyloxy radical.

10. A process as claimed in claim 6, carried out substantially as described in the Example herein.

11. A compound as claimed in claim 1, whenever prepared by a process as claimed in any one of claims 6 to 10.

12. A salt of a compound claimed in claim 1, whenever prepared by a process as claimed in any one of claims 6 to 10.

13. A physiologically tolerable salt of a compound claimed in claim 1, whenever prepared by a process as claimed in any one of claims 6 to 10.

14. A pharmaceutical preparation which comprises a compound as claimed in any one of claims 1 to 3, 5, 11 and 13, in admixture or conjunction with a pharmaceutically suitable carrier.

15. A pharmaceutical preparation as claimed in claim 14, which is in dosage unit form.

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